REMARKS

Claims 12-25 and 30-42, which were previously withdrawn from consideration, have been canceled by the present amendment. Claims 1-11 and 26-29 are pending.

Allowable Subject Matter

Applicants note with appreciation the Examiner's statement that "[c]laims 8-11 and 26-29 are allowable" (Office action at page 3).

Rejections under 35 U.S.C. § 103(a)

Claims 1-7 were rejected as obvious over Strehlau *et al.* (*Proc. Natl. Acad. Sci. USA*, 94:695-700, 1997; "Strehlau") in view of Jeyarajah *et al.* (*Transplantation Proceedings*, 27(1):887-889, 1995; "Jeyarajah").

Two of the rejected claims, claims 1 and 4, are independent claims. Claim 1 covers a method for evaluating acute transplant rejection in a host by determining the magnitude of gene expression in a fluid test sample obtained from the host. At least two genes are analyzed, and the claim requires those genes to be selected from one or more of the following gene clusters: the pro-apoptotic cluster, the cytoprotective cluster, the IL-7/17 cluster, the IL-8 cluster, the IL-10 cluster, the IL-15 cluster and the T cell cluster. With respect to a baseline measurement, upregulation of the two (or more) genes indicates acute transplant rejection. The other independent claim, claim 4, also covers a method of evaluating acute transplant rejection. Claim 4 requires analysis of at least two genes of a pro-apoptotic gene cluster in a urine sample.

Turning to the references, the Examiner characterizes Strehlau as a study of "intragraft expression of IL-7, IL-10, IL-15 and Fas ligand" "during acute renal allograft rejection" (Office action at page 3). The Examiner recognizes that Strehlau does "not disclose the fluid test sample from a host" (Office action at page 3). The Examiner argues, however, that one of ordinary skill in the art would have been motivated to use such a sample based on the teaching of the secondary reference, Jeyarajah, "because cytokine message was easily detected in the urinary sediment of renal allograft recipients regardless of acute cellular rejection" (Office action at

page 3, citing Jeyarajah at page 887, column 2, second paragraph). The Examiner then concludes that:

> It would have been prima facie obvious to apply urine samples for evaluating acute transplants [*sic*] rejection by determining a magnitude of gene expression in the fluid test sample of at least two genes which are selected from one or more gene clusters, the IL-7/17 cluster, the IL-8 cluster, the IL-10 cluster, and the T cell cluster. (Office Action at page 3, lines 9-16).

This ground for rejection is respectfully traversed. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. And third, the prior art reference (or references when combined) must teach or suggest all of the limitations of an Applicant's claims. Moreover, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. MPEP at 2143, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In the present case, Strehlau examined immune activation markers in renal graft biopsies. As the Examiner acknowledged, Strehlau is limited to analysis of graft tissue; there is no suggestion to use a fluid test sample from the host. In fact, Strehlau suggests that such methods may not be successful. Strehlau states:

> RT-PCR has been performed on RNA from fine needle aspirations (40, 41), peripheral blood, and urine sediments (42) …All of these techniques offer a less invasive approach than core biopsies, *but it remains to be determined whether the same reliability can be achieved.* (Strehlau, page 699, right column, fourth full paragraph; emphasis added).

The paper Strehlau cites in this passage following the reference to "peripheral blood, and urine sediments" -- reference (42) -- is Jeyarajah. Thus, Strehlau not only expressed uncertainty about using samples other than core biopsies, he expressed that uncertainty specifically in view of the results obtained by Jeyarajah. It is true that Jeyarajah was able to detect cytokine message in urinary sediment, but one of ordinary skill in the art would not have been motivated to carry

out the methods now claimed on that basis, even when Jeyarajah's teaching is combined with Strehlau's.

More specifically, Jeyarajah used PCR to look for transcripts of various cytokines in three different types of samples (urine sediment, peripheral blood, and kidney biopsy) *at the time of diagnosis* of acute cellular rejection (ACR) *and after* successful therapy for ACR (*see* Materials and Methods at page 887). The results obtained from the samples were variable. One cytokine, IL-5, "showed the most consistent differences pre- and post rejection therapy." IL-5 was not consistent, it was just "the most consistent" of the cytokines tested before and after therapy. Jeyarajah states that in peripheral blood, "IL-5 was detected in only 6 of the 10 patients at the time of diagnosis of ACR, but showed a reduction in five of these patients after successful antirejection therapy" (page 887, second column). In urine, however, IL-5 *increased* (see page 888, right-hand column, where Jeyarajah hypothesizes as to the reason why these transcripts might decrease in the blood but increase in urine). In the biopsied tissue "IL-5 showed a mixed pattern, with 4 of 8 patients showing increased message" (bridging pages 887-888). With regard to some of the other cytokines, IL-6 showed a mixed pattern, and IFN-γ and IL-2 showed statistically insignificant differences (Jeyarajah, page 887, right column, first full paragraph). Not a single marker was both detected in all three types of samples and showed a correlation with transplant therapy. One of ordinary skill in the art, upon reading Jeyarajah, even in view of Strehlau, would not have been motivated to carry out the method now claimed, nor is there any indication in the prior art that one would have had a reasonable expectation for success. Jeyarajah did observe cytokines in blood and urine in patients who had received an allograft, but that is not enough. Applicants fail to see, and the record does not establish, how one would be motivated to assess, in a fluid sample, at least two of the genes within the clusters recited in claims 1 and 4, nor how one would recognize upregulation of those "at least two" genes as an indication of acute transplant rejection (also as recited in claims 1 and 4). There is no reasonable expectation for success in the prior art. Strehlau's work is strictly limited to graft tissue; Strehlau expressed skepticism that peripheral blood and urine sediment, as studied by Jeyarajah, would prove reliable; and Jeyarajah reported inconsistent and variable expression profiles in the context

of an antirejection therapy. Applicants respectfully request that the rejection of claims 1-7 as obvious over Strehlau and Jeyarajah be withdrawn.

Concluding Remarks

In view of the foregoing, Applicants contend that the present claims are now in condition for allowance, which action is respectfully requested. Should the Examiner find a telephone conference helpful in resolving any remaining issues, the undersigned is available at the number shown below.

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing attorney docket number 01948-061001.

Respectfully submitted,

Date: December 14 2005

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